Synthesis of Crown Compounds Containing a 1,3,4-Oxadiazole Moiety: Microwave-Assisted Synthesis

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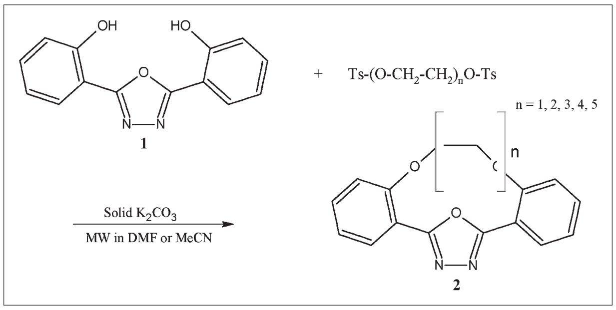
Received February 5, 2009
DOI 10.1002/jhet.201



New macrocyclic polyether compounds containing a 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole moiety are quickly prepared by a nucleophilic substitution reaction involving ethylene glycol ditosylate or polyethylene glycol ditosylate and a biphenol, the 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole, with solid anhydrous potassium carbonate as a base under microwave irradiation (monomode and multimode). The structures of new macrocyclic polyether compounds were confirmed by ^{1}H, ^{13}C NMR, mass spectrometry, and elemental analysis.

J. Heterocyclic Chem., **47**, 555 (2010).

INTRODUCTION

The design and synthesis of artificial hart mimics possessing specific weak interactions and complexation properties to ion and neutral molecules has inspired many scientists during the past decades [1,2]. The Pedersen's [3] synthesis of crown ethers and the demonstrated ability of these molecules to chelate cations launched a whole search for further novel polyether macrocyclic structures that promote similar recognition phenomena [4]. The 1,3,4-oxadiazole ring is very rigid and as for the crown compounds containing a 1,3,4-thiadiazole moiety [5], the macrocyclic polyether containing it has potentially planar conformation [6]. A synthesis of such compounds containing 1,3,4-oxadiazole moiety has been previously effectuated by condensation of ethylene glycol or polyethylene glycol derivatives with the 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole by direct displacement reaction of halide with the bisphenolate and using the classical heating process. This synthesis requires long reaction time, and poor yields were obtained [7]. No macrocyclic compounds were found when we tried the heterocyclisation of the 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole with ethylene glycol ditosylate or polyethylene glycol ditosylate under classical heating using a previously described procedure [5]. In this article we report the microwave-assisted synthesis of crown compounds containing a 1,3,4-oxadiazole moiety.

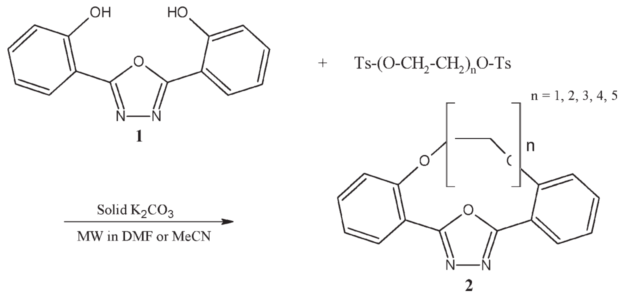
RESULTS AND DISCUSSION

Macrocyclic compounds **2a–d** were prepared by a nucleophilic substitution reaction involving a glycol ditosylate with the bisphenoloxadiazole (1) (Scheme 1). This reaction was easily achieved by microwave irradiation and the macrocycles **2a–d** were obtained in moderate yields and excellent state of purity as in ref. 6 (Table 1).

A good achievement of this synthesis requires longer times (9 h) under irradiation using multimode microwave reaction compared with monomode one (2 h). However, no reaction product has been isolated using classical conventional heating.

To understand the pathway mechanisms that occur in the nucleophilic substitution reaction for cyclization of ditosyl polyether, quantum calculations at density functional theory (DFT) level were performed with thiadiphenol, both in vacuum and acetonitrile solvent, using polarized continuum method (PCM) method. The obtained results in the case of 1,3,4-thiadiazole moiety

Scheme 1. Synthesis of marcocyclic compounds containing a 1,3,4-oxadiazole moiety.



are analyzed in term of electronic energy of the calculated molecule conformations [6].

Specific microwave effect was observed in this reaction, the polarity is increased during the reaction from the ground state toward the transition state, and the stabilization of the transition state is more effective than that of the ground state (Scheme 2), this result in an enhancement of reactivity by a decrease in the activation energy [8].

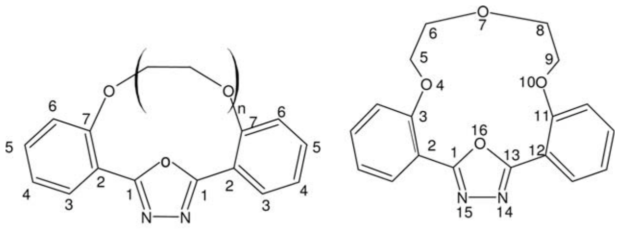
Using the monomode irradiation process, the notable enhancement in the yields of the crown compounds synthesis, and the shorter time of the reaction, can be explained by the fact that the microwaves are focused through a wave guide on the reaction vessel. The power density is, therefore, higher than using a multimode microwave apparatus.

EXPERIMENTAL

Melting points were determined with on an IA 9000 series electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker F.T. AC 300 spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) using chloroform-d$_1$ (CDCl$_3$) as solvent. Matrix-assisted laser desorption ionization (MALDI) and time-of-flight mass spectrometry (TOF-MS) are used to record the mass spectra of the macrocyclic polyether compounds **2a–d**. Elemental analyses were performed by the elemental analysis service of CNRS, Vernaison, France. All starting materials were of reagent grade and used as purchased.

General procedure for the synthesis of macrocycles 2a–d. A mixture of 2,5-bis(2-hydroxyphenyl)-1,3,4-oxadiazole **1** (0.75 g, 2.95 mmoles), anhydrous potassium carbonate (1.65 g, 12 mmoles), and ethylene glycol ditosylate or polyethylene glycol ditosylate (2.78 mmoles) in 30 mL of a nonprotic polar solvent, such as DMF or acetonitrile, was introduced into a fluoropolymeric cylindrical flask placed in a MARS5 XP-1500 PLUS CEM multimode microwave and irradiated for 9 h (300 W) at 150°C or irradiated for 2 h (150 W) in a CEM monomode microwave in DMF at 150°C with vigorous stirring. The precipitate was heated under reflux with 20 mL of aqueous potassium hydroxide solution for 1 h to destroy the unreacted tosylate, oxadiazole derivative **1**, or the open-chain intermediate of **2**. After cooling, the crude product was filtered, washed with water, recrystallized from ethanol, and dried under high vacuum. Yields, melting points, and results of the elemental analysis (C, H, and N) for compounds **2a–d** were given in Table 1.

The general formula of the parent macrocyclic compound with corresponding numbering scheme is given later. Localization of the methylene groups in the polyether macrocycle has been made using the International Union of Pure and Applied Chemistry rules concerning the different bicyclic systems.



Numbering used for the Localization of aromatic carbon

Example of the numbering used for the bicyclic systems (**2a**)

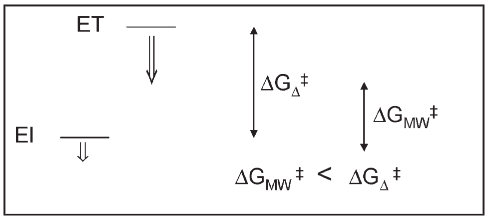
2,3,11,12-Dibenzo-4,7,10,16-tetraoxa-14,15-diazabicyclo[11.2.1]-hexadeca-13,15-diene (2a). ^{1}H NMR (CDCl$_3$): δ (ppm) 3.95–3.99 (m, 4H, CH$_2$ (6) and CH$_2$ (8)), 4.26–4.29 (m, 4H, CH$_2$ (5) and CH$_2$ (9)), 7.01 (d, J = 8.6 Hz, 2H, 6-H), 7.08 (dd, J = 7.7 Hz, 2H, 4-H), 7.48 (dd, J = 7.9 Hz, 2H, 5-H), 8.11 (d, J = 7.7 Hz, 2H, 3-H). ^{13}C NMR (CDCl$_3$): δ (ppm) 61.5 (CH$_2$ (5) and CH$_2$ (9)), 63.4 (CH$_2$ (6) and CH$_2$ (8)), 110.8 (C$_6$),

Table 1

Physical and analytical data of compounds **2a–d**.

Compound	Yield (%)				Analysis (%) found/calcd.		
	Monomode (2 h)	Multimode (9 h)	Mp (°C)	Molecular formula	C	H	N
2a (n = 2)	47	36	175	$C_{18}H_{16}N_2O_4$	66.52	5.10	8.71
					66.66	4.97	8.64
2b (n = 3)	51	33	200	$C_{20}H_{20}N_2O_5$	65.01	5.63	7.84
					65.21	5.47	7.60
2c (n = 4)	42	30	185	$C_{22}H_{24}N_2O_6$	63.95	6.06	6.82
					64.07	5.87	6.79
2d (n = 5)	39	27	187	$C_{24}H_{28}N_2O_7$	62.98	6.33	6.27
					63.15	6.18	6.14

Scheme 2



113.5 (C_4), 122.5 (C_2), 127.2 (C_3), 138.6 (C_5), 150.1 (C_7), 163.4 (C_1-oxadiazole). MALDI-TOF-MS: *m*/*z* 325 (M +1).

2,3,14,15-Dibenzo-4,7,10,13,19-pentaoxa-17,18-diazabicyclo[14.2.1]nonadeca-16,18-diene (2b). ^{1}H NMR ($CDCl_3$): δ (ppm) 3.54 (s, 4H, CH2 (8) and CH_2 (9)), 3.87–3.91 (m, 4H, CH_2 (6) and CH_2 (11)), 4.24–4.28 (m, 4H, CH_2 (5) and CH_2 (12)), 7.04 (d, *J* = 8.3 Hz, 2H, 6-H), 7.08 (dd, *J* = 8.0 Hz, 2H, 4-H), 7.49 (dd, *J* = 8.0 Hz, 2H, 5-H), 7.90 (d, *J* = 7.6 Hz, 2H, 3-H). ^{13}C NMR ($CDCl_3$): δ (ppm) 60.3 (CH_2 (5) and CH_2 (12)), 62.7 (CH_2 (8) and CH_2 (9)), 73.2 (CH_2 (6) and CH_2 (11)), 108.1 (C_6), 114.5 (C_4), 121.3 (C_2), 126.3 (C_3), 138.3 (C_5), 152.8 (C_7), 164.0 (C_1-oxadiazole). MALDI-TOF-MS: *m*/*z* 369 (M + 1).

2,3,17,18-Dibenzo-4,7,10,13,16,22-hexaoxa-20,21-diazabicyclo[17.2.1]docosa-19,21-diene (2c). ^{1}H NMR ($CDCl_3$): δ (ppm) 3.61–3.68 (m, 8H, CH_2 (8, 9, 11, and 12)), 4.11 (t, *J* = 5.6 Hz, 4H, CH_2 (6) and CH_2 (14)), 4.33 (t, *J* = 5.6 Hz, 4H, CH_2 (5) and CH_2 (15)), 7.04 (d, *J* = 8.6 Hz, 2H, 6-H), 7.13 (dd, *J* = 7.5 Hz, 2H, 4-H), 7.45 (dd, *J* = 7.8 Hz, 2H, 5-H), 8.53 (d, *J* = 8.5 Hz, 2H, 3-H). ^{13}C NMR ($CDCl_3$): δ (ppm) 60.3 (CH_2 (5) and CH_2 (15)), 61.4 (CH_2 (6) and CH_2 (14)), 63.1 (CH_2 (8) and CH_2 (12)), 64.0 (CH_2 (9) and CH_2 (11)), 108.8 (C_6), 115.4 (C_4), 123.1 (C_2), 128.72 (C_3), 135.0 (C_5), 153.4 (C_7), 165.5 (C_1-oxadiazole). MALDI-TOF-MS: *m*/*z* 413 (M + 1).

2,3,20,21-Dibenzo-4,7,10,13,16,19,25-heptaoxa-23,24-diazabicyclo[20.2.1]pentacosa-22,24-diene (2d). ^{1}H NMR ($CDCl_3$): δ (ppm) 3.56 (s, 4H, CH_2 (11) and CH_2 (12)), 3.56–3.78 (m, 8H, CH_2 (9), CH_2 (14), CH_2 (17) and CH_2 (18)), 4.09 (t, *J* = 5.1 Hz, 4H, CH_2 (6) and CH_2 (17)), 4.38 (t, *J* = 5.1 Hz, 4H, CH_2 (5) and CH_2 (18)), 7.08 (d, *J* = 7.5 Hz, 2H, 6-H), 7.13 (dd, *J* = 6.7 Hz, 2H, 4-H), 7.44 (dd, *J* = 7.0 Hz, 2H, 5-H), 8.54 (d, *J* = 8.4 Hz, 2H, 3-H). ^{13}C NMR ($CDCl_3$): δ (ppm) 60.8 (CH_2 (5) and CH_2 (18)), 62.6 (CH_2 (6) and CH_2 (17)), 64.1 (CH_2 (8) and CH_2 (15)), 64.1 (CH_2 (9, 11, 12 and 14), 108.9 (C_6), 114.9 (C_4), 122.0 (C_2), 126.5 (C_3), 138.8 (C_5), 152.7 (C_7), 164.7 (C_1-oxadiazole). MALDI-TOF-MS: *m*/*z* 457 (M + 1).

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